LENVIMA® (lenvatinib)

United States Food and Drug Administration
Pediatric Oncology Subcommittee of the
Oncologic Drugs Advisory Committee

November 19, 2015

Eisai

LENVIMA® (lenvatinib)

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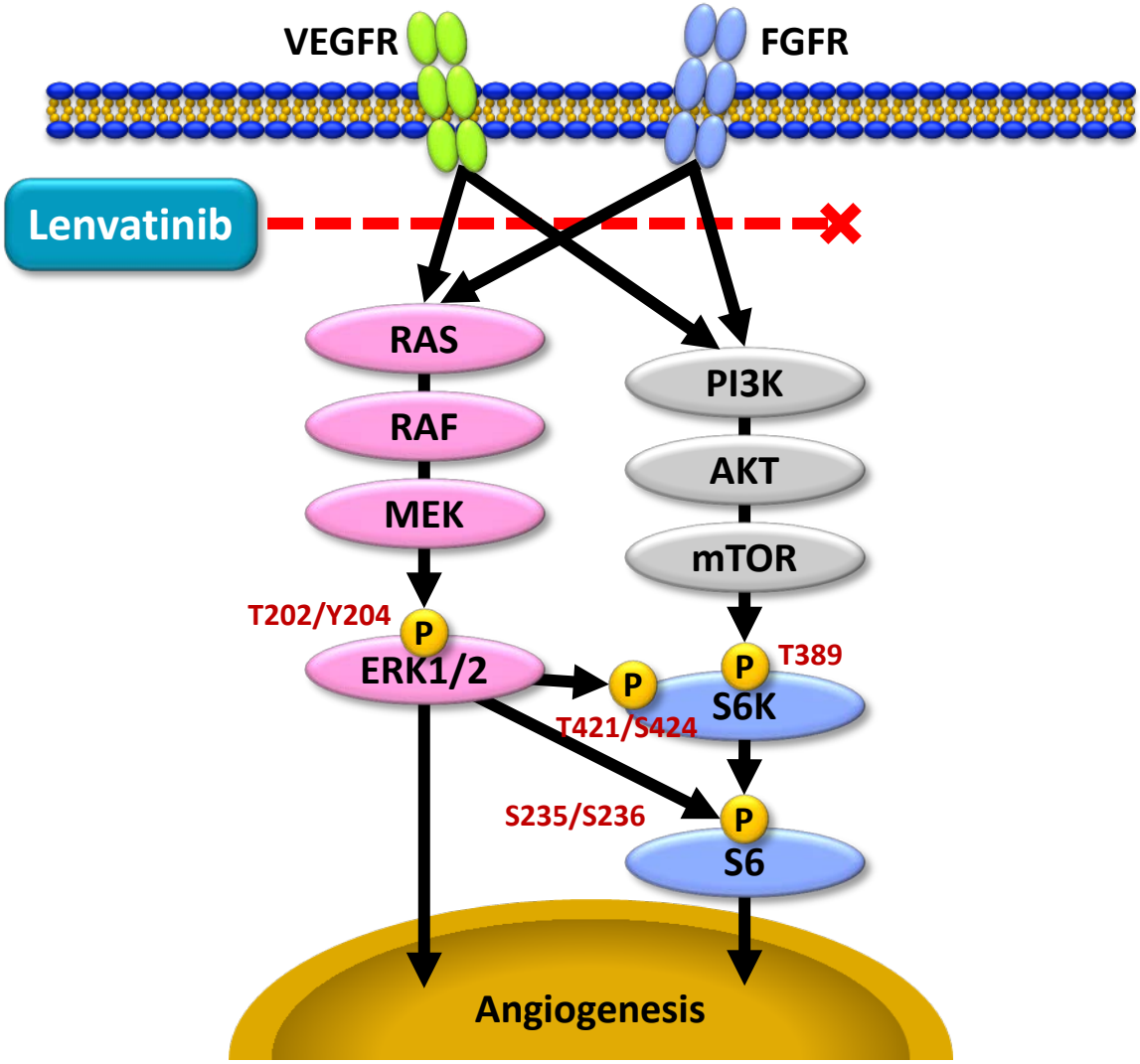
Why Are We Here Today?

- Seeking a Written Request from the FDA for pediatric development of lenvatinib in the United States
- Lenvatinib is a novel receptor tyrosine kinase (RTK) inhibitor with potent activity against both VEGF and FGF receptors
- Lenvatinib is approved for the treatment of thyroid cancer in the United States, European Union, and Japan
- Lenvatinib has also demonstrated impressive activity in combination with everolimus for advanced RCC
- We are here today to discuss the rationale for investigating lenvatinib in pediatric cancer

Agenda

- Introduction to lenvatinib
- Adult clinical development program
- Pediatric development program

Mechanism of Action of Lenvatinib

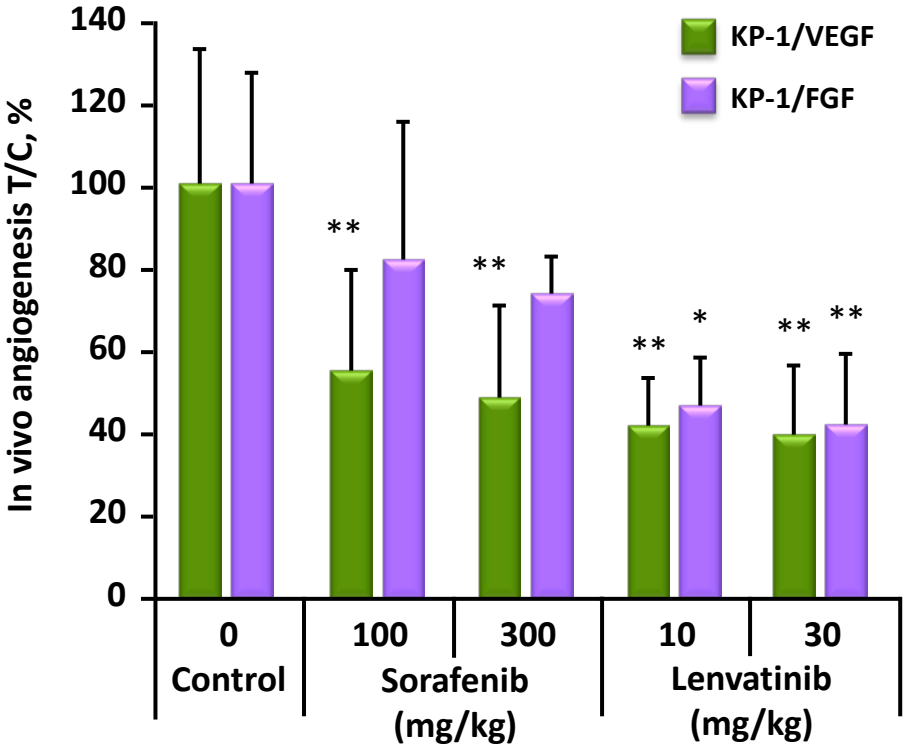


Adapted from Stjepanovic N, Capdevila J. *Biologics: Targets and Therapy.* 2014:8;129-139; Eisai data on file.

Lenvatinib Is a Potent Tyrosine Kinase Inhibitor Active Against Both VEGF and FGF Receptors

	IC_{50}, nM	
Target	**Lenvatinib**	**Sorafenib**
VEGFR3	2.3	16
VEGFR2	3.0	21
VEGFR1	4.6	21
RET	6.4	15
PDGFR-α	29	1.6
FGFR2	27	150
FGFR4	43	3400
FGFR3	52	340
FGFR1	61	340
KIT	85	140

Lenvatinib, but not sorafenib, significantly inhibits both VEGF-driven and FGF-driven angiogenesis



* P<0.05; ** P<0.01 compared to vehicle.

Adapted from Yamamoto Y, et al. *Vascular Cell.* 2014;6:18.

Summary of Nonclinical Toxicology/Safety Pharmacology and Clinical Pharmacology

- Nonclinical toxicology and safety pharmacology findings consistent with other VEGFR inhibitors
- Toxicity profile in juvenile and adult rats similar, although onset of toxicity and mortality occurred earlier in juvenile rats
- Linear PK and minimal accumulation at clinically relevant doses
- Extensively metabolized with no major metabolites
- Elimination half-life approximately 28 hours
- No clinically significant drug-drug interactions
- No food effect
- Does not prolong QTc interval in healthy volunteers (increases >10 msec excluded)

Clinical Development Program in Adults (N>2400)

Phase 1: Dose and Schedule Selection Studies

Phase 2 Studies (monotherapy)
- Thyroid
- Hepatocellular
- Glioblastoma
- Endometrial
- Melanoma
- NSCLC
- ATC/MTC Japan
- RET/KIF5B – NSCLC

Phase 1b/2 Studies (combination)
- NSCLC (carbo/paclitaxel)
- Melanoma (TMZ/DTIC)
- mRCC (everolimus)
- Ovarian (gem/carbo)
- Melanoma (DTIC)
- Solid tumors (golvatinib)
- Solid tumors (pembrolizumab)

Supporting Studies
- Bioavailability
- QTc study
- Food effect
- DDI studies
- Renal impairment
- Hepatic impairment
- Bioequivalence
- Mass Balance

Phase 3 Study:
Differentiated Thyroid Cancer (303)
COMPLETED

Phase 3 Study:
Hepatocellular Carcinoma (304)
ENROLLMENT COMPLETE

Approved

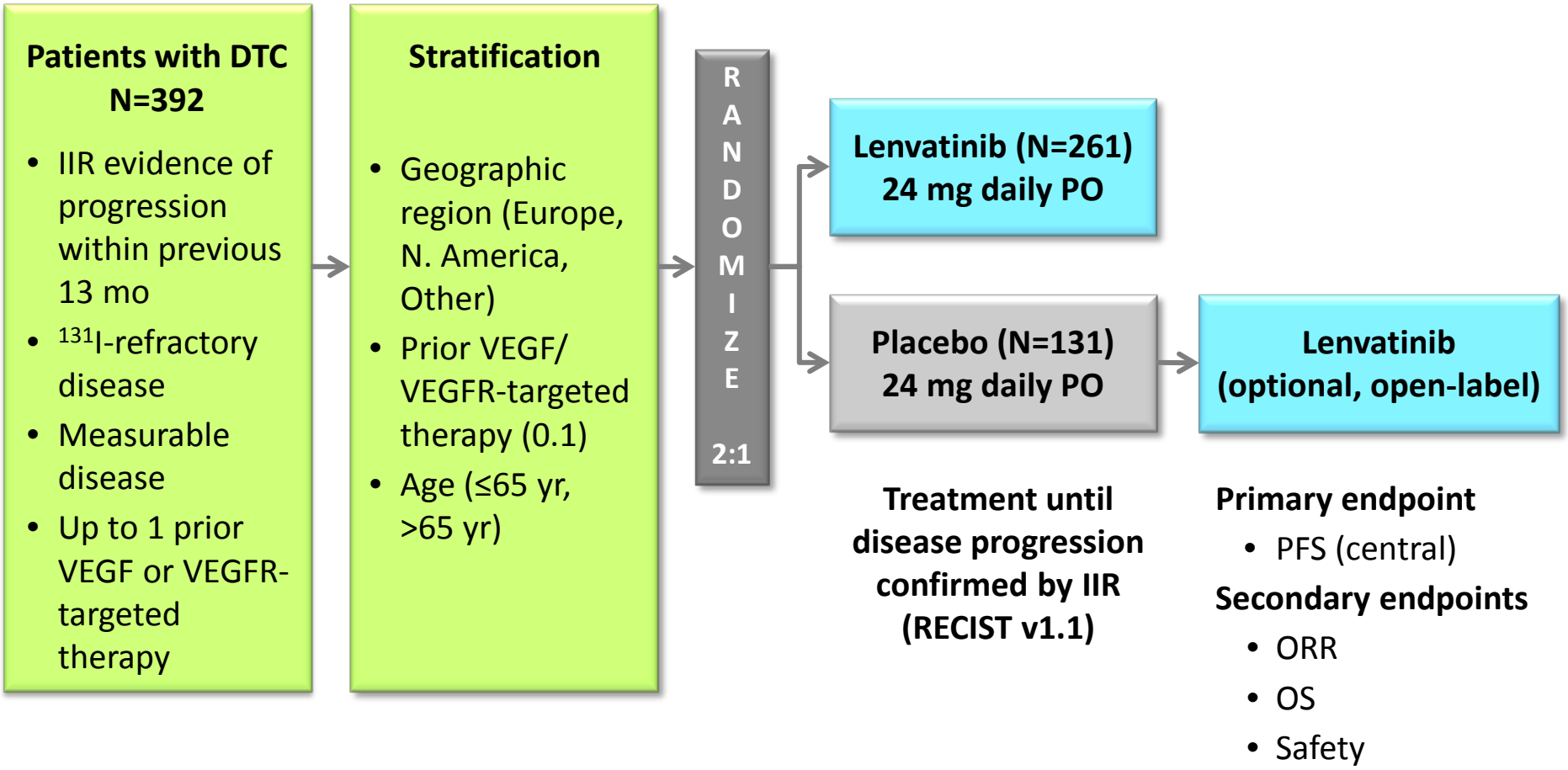
Global, Randomized, Phase 3 Trial in Radioiodine-Refractory Differentiated Thyroid Cancer

Study 303

Eisai

Global, Randomized, Double-Blind, Pivotal Trial in ^{131}I-Refractory DTC

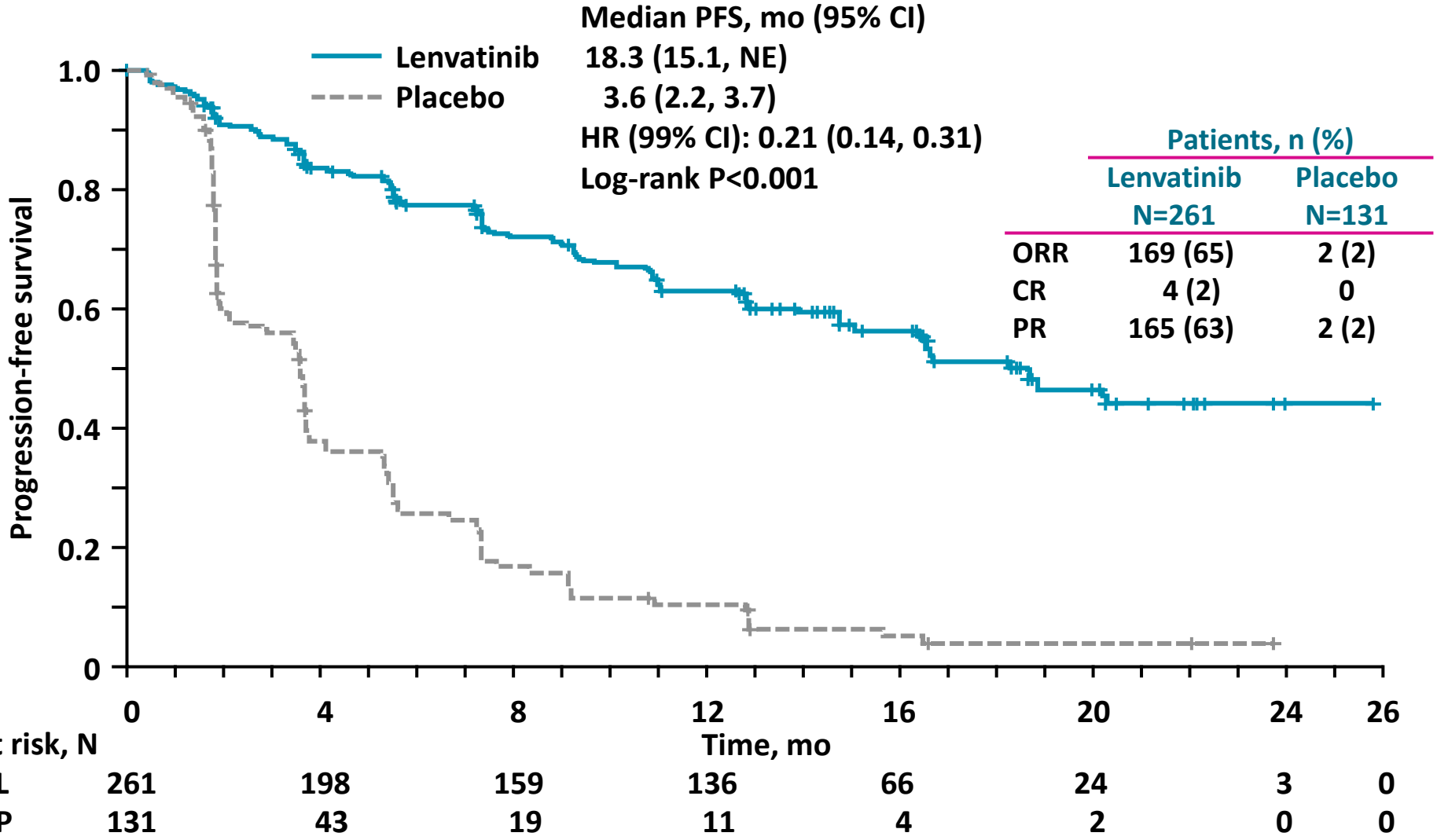
Study 303



DTC=differentiated thyroid cancer; ^{131}I=radioactive iodine; IIR=independent imaging review; ORR=objective response rate; OS=overall survival; PO=by mouth; RECIST=Response Evaluation Criteria in Solid Tumors.

Progression-Free Survival (Independent Review) and Objective Response Rate

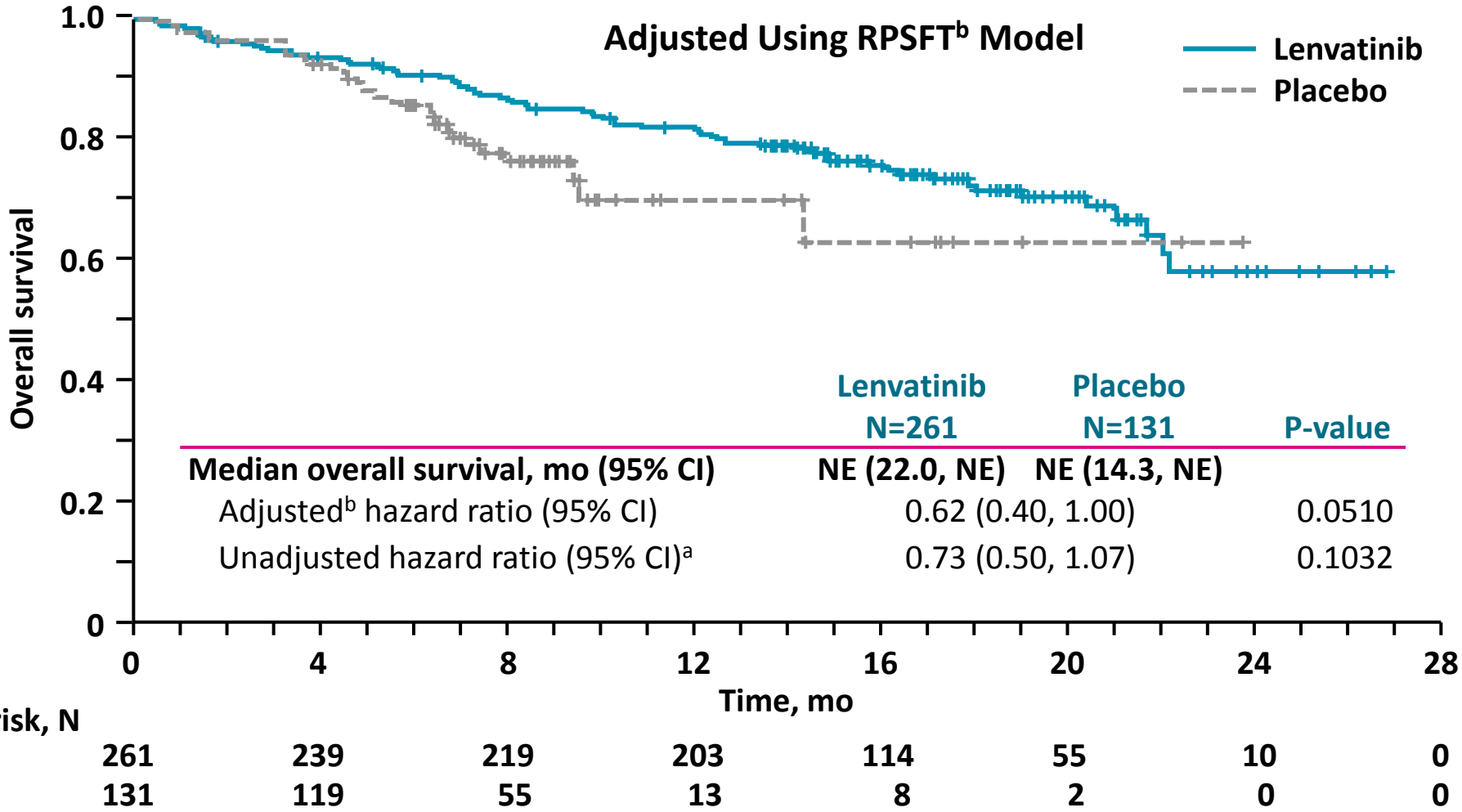
Study 303



Patients, n (%)	Lenvatinib N=261	Placebo N=131
ORR	169 (65)	2 (2)
CR	4 (2)	0
PR	165 (63)	2 (2)

Overall Survival

Study 303



	Lenvatinib N=261	Placebo N=131	P-value
Median overall survival, mo (95% CI)	**NE (22.0, NE)**	**NE (14.3, NE)**	
Adjusted[b] hazard ratio (95% CI)	0.62 (0.40, 1.00)		0.0510
Unadjusted hazard ratio (95% CI)[a]	0.73 (0.50, 1.07)		0.1032

At risk, N

L	261	239	219	203	114	55	10	0
P	131	119	55	13	8	2	0	0

[a] Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 yr vs >65 yr), and previous VEGF/VEGFR-targeted therapy (0 vs 1).

[b] Rank Preserving Structural Failure Time.

Overview of Safety

Study 303

	Lenvatinib N=261	Placebo N=131
Median duration of treatment, mo	16.1	3.9
Patient-year of exposure	269.45	65.38
SAE, n (%)	139 (53.3)	31 (23.7)
Fatal AE, n (%)	20 (7.7)	6 (4.6)
TEAEs by treatment duration		
Total duration of treatment, yr	298.8	67.1
SAE, n (AE rate)	291 (0.97)	55 (0.82)
TEAE leading to treatment discontinuation, n (%)	46 (17.6)	6 (4.6)
TEAE leading to study drug modification, n (%)		
Dose reduction and/or interruption	234 (89.7)	25 (19.1)
Dose reduction	178 (68.2)	6 (4.6)
Dose interruption	217 (83.1)	24 (18.3)

Treatment-Emergent Adverse Events (>30%) With a Between-Group Difference ≥5%

Study 303

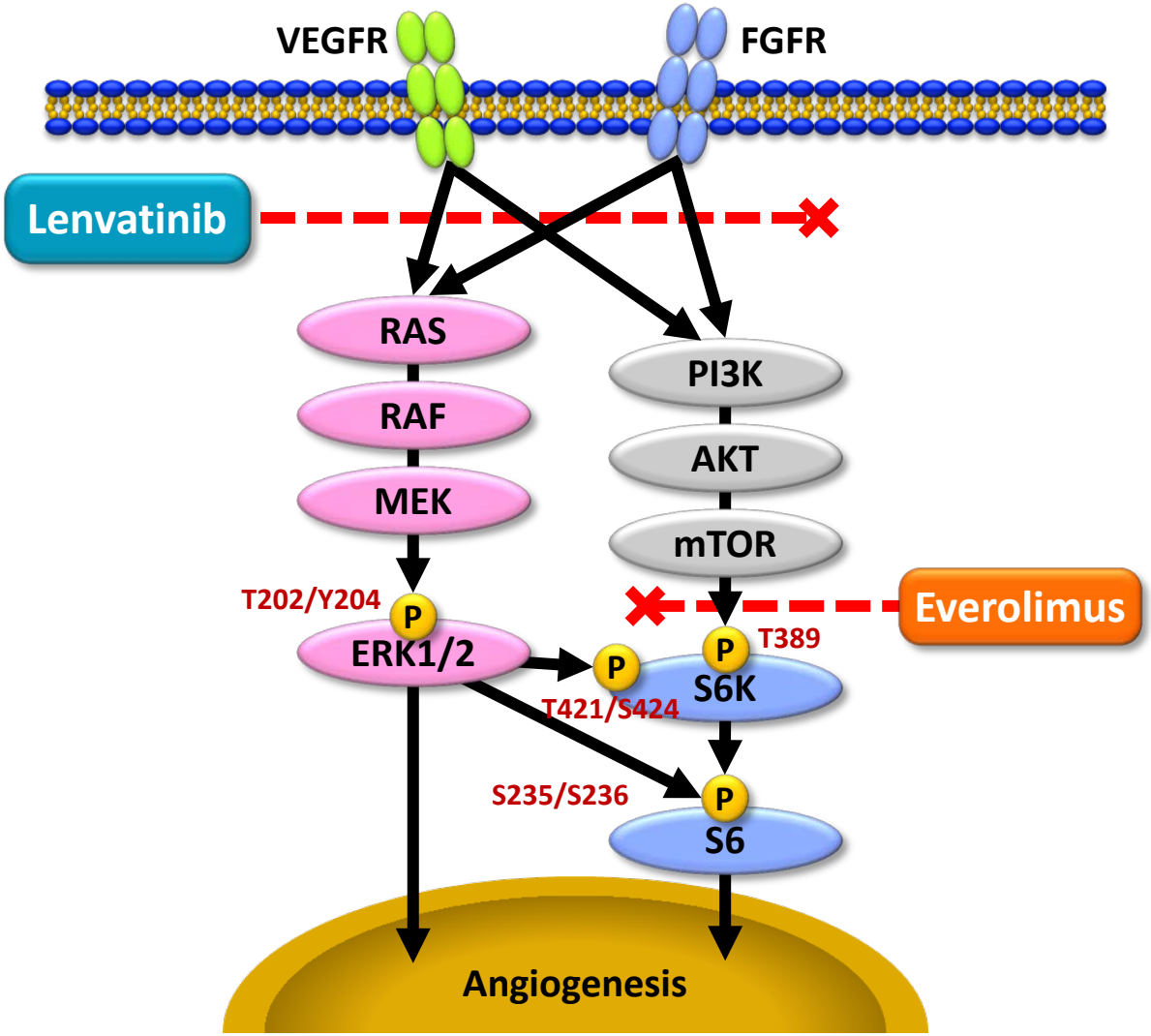
	TEAEs, %			
	Lenvatinib N=261		Placebo N=131	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hypertension	73	44	16	4
Diarrhea	67	9	17	0
Fatigue/asthenia	67	11	35	4
Arthralgia/myalgia	62	5	28	3
Decreased appetite	54	7	18	1
Weight decreased	51	13	15	1
Nausea	47	2	25	1
Stomatitis	41	5	8	0
Headache	38	3	11	1
Vomiting	36	2	15	0
Proteinuria	34	11	3	0
PPE syndrome	32	3	1	0
Abdominal pain	31	2	11	1
Dysphonia	31	1	5	0

PPE=Palmar-plantar erythrodysesthesia.

Rationale for Combining Lenvatinib With Everolimus

Eisai

Proposed Mechanism of Interaction Between Lenvatinib and Everolimus



Adapted from Stjepanovic N, Capdevila J. *Biologics: Targets and Therapy.* 2014:8;129-139; Eisai data on file.

Randomized, Phase 2 Trial in Combination With Everolimus in Renal Cell Carcinoma

Study 205

Eisai

Study 205 in Renal Cell Carcinoma

An open-label, randomized, multicenter study (56 sites)

153 patients

- Unresectable advanced or metastatic RCC
- Progression on or within 9 mo of stopping prior tx
- 1 prior progression on or after prior VEGF or VEGFR-targeted therapy
- Measurable disease
- ECOG PS ≤1

RANDOMIZE

- **Lenvatinib 18 mg orally qd + Everolimus 5 mg orally qd**
- **Lenvatinib 24 mg orally qd**
- **Everolimus 10 mg orally qd**

Primary endpoint

- PFS (by InvR)

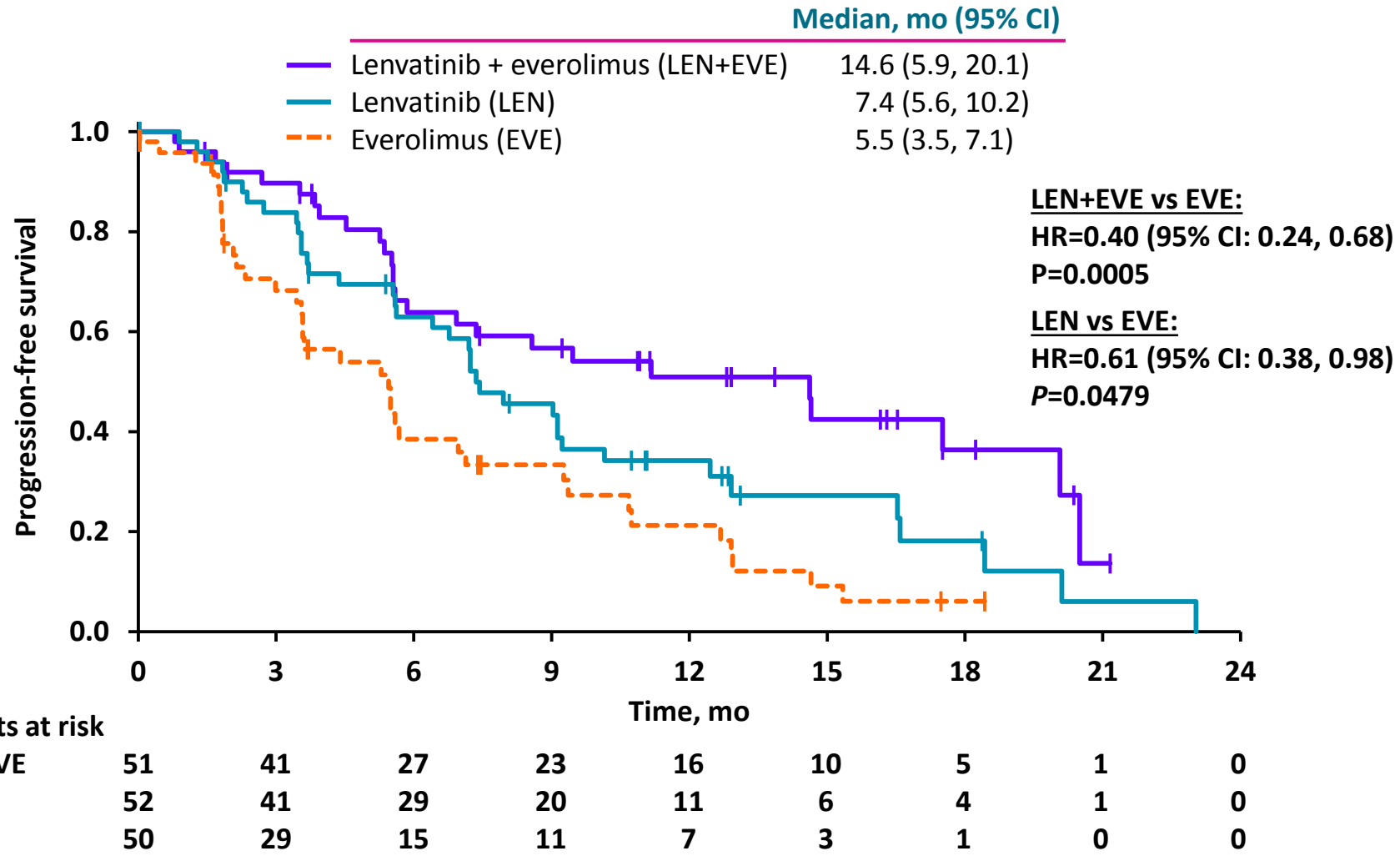
Secondary endpoints

- OS
- ORR
- Disease control rate
- Stable disease
- CBR
- PK/PD

- Enrollment period: March 2012 - July 2013
- Data Cut-off for primary analysis: June 13, 2014 (when the 90th PFS event occurred)
- Primary Data Analysis was presented at ASCO 2015

Progression-Free Survival by Investigator

Study 205



Patients at risk									
LEN+EVE	51	41	27	23	16	10	5	1	0
LEN	52	41	29	20	11	6	4	1	0
EVE	50	29	15	11	7	3	1	0	0

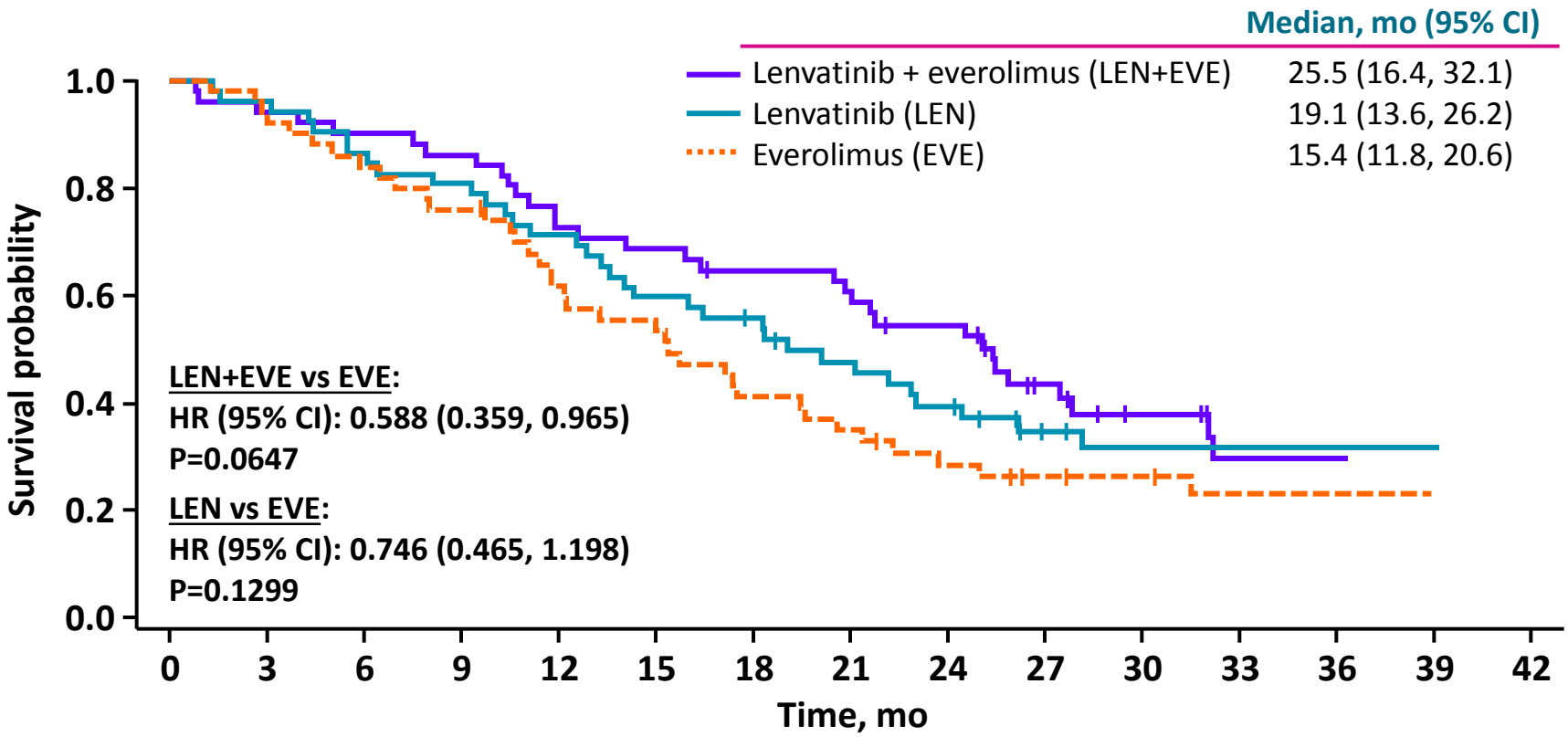
Tumor Response (Investigator Assessment)

Study 205

	Lenvatinib + everolimus N=51	Lenvatinib N=52	Everolimus N=50
Objective response rate (CR + PR)	**43%**	**27%**	**6%**
Complete response (CR)	2%	0	0
Partial response (PR)	41%	27%	6%
Median duration of response, mo	13.0	7.5	8.5
(95% CI)	(3.7, NE)	(3.8, NE)	(7.5, 9.4)

Overall Survival Update

Study 205 (Data Cut-off: Date July 31, 2015)



Patients at risk:

LEN+EVE	51	48	46	44	37	35	32	30	26	17	11	7	2	0	0
LEN	52	50	45	42	37	31	28	23	19	12	7	3	2	1	0
EVE	50	46	42	38	30	27	20	17	13	10	9	5	1	0	0

Treatment-Emergent Adverse Events ≥30% by Preferred Term

Study 205

	Patients, %					
	LEN 18 mg + EVE 5 mg N=51		Lenvatinib 24 mg N=52		Everolimus 10 mg N=50	
Preferred term	Any grade	Grade 3 [4]	Any grade	Grade 3 [4]	Any grade	Grade 3 [4]
Any TEAE	**100**	**77[a]**	**100**	**89[a]**	**100**	**54[a]**
Diarrhea	84	20	71	12	34	2
Decreased appetite	53	6	58	4	18	0
Fatigue	51	12	40	8	32	0
Vomiting	47	8	39	4	12	0
Nausea	43	6	62	8	16	0
Hypertension	41	14	48	17	10	2
Cough	39	0	17	2	30	0
Hypertriglyceridemia	35	10	14	4	24	8
Hypercholesterolemia	35	2	12	0 [2]	16	0
Weight decreased	31	2	50	6	8	0
Stomatitis	29	0	25	2	42	2

[a] **Grade ≥ 3.**

Comprehensive Pediatric Development Program

Rationale for Lenvatinib in Pediatric Cancer

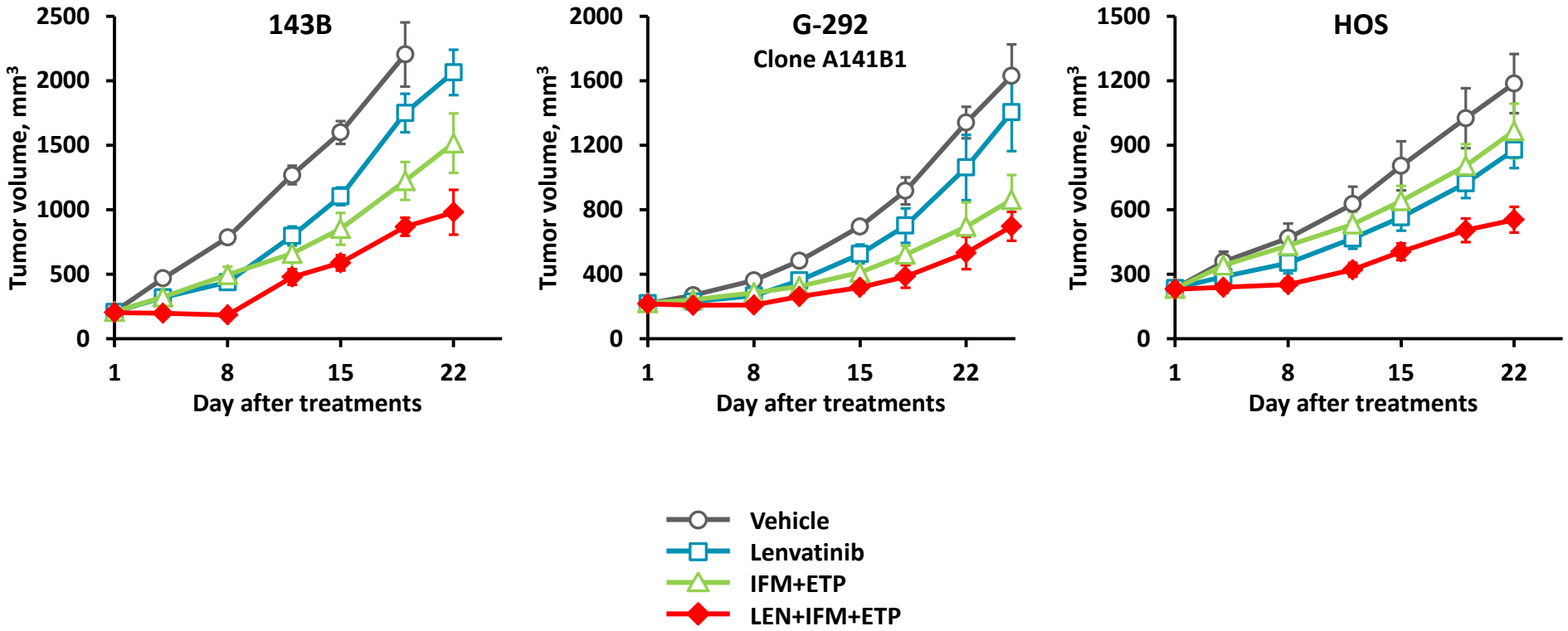
- Clear unmet medical need in pediatric cancers
- Lenvatinib inhibits both VEGFR and FGFR activity
  - Relevant target in pediatric cancer, particularly in sarcoma
- Other RTK inhibitors have consistently demonstrated activity in preclinical models of pediatric solid tumors (cediranib, sorafenib, sunitinib, and pazopanib)

Rationale for Combination With Everolimus in Pediatric Cancer

- mTOR inhibitors have also demonstrated activity in pediatric tumors, including sarcoma
- Pro-angiogenic signaling pathways (VEGF, FGF) cooperate with mTOR-mediated regulation of cell growth and maintenance to drive the development of pediatric solid tumors
- The combination of VEGF and mTOR pathway inhibition
  - May abrogate several alternative signaling pathways
  - Has shown promise in preclinical solid tumor models
- The combination has demonstrated activity compared with everolimus alone with a manageable safety profile in adult RCC

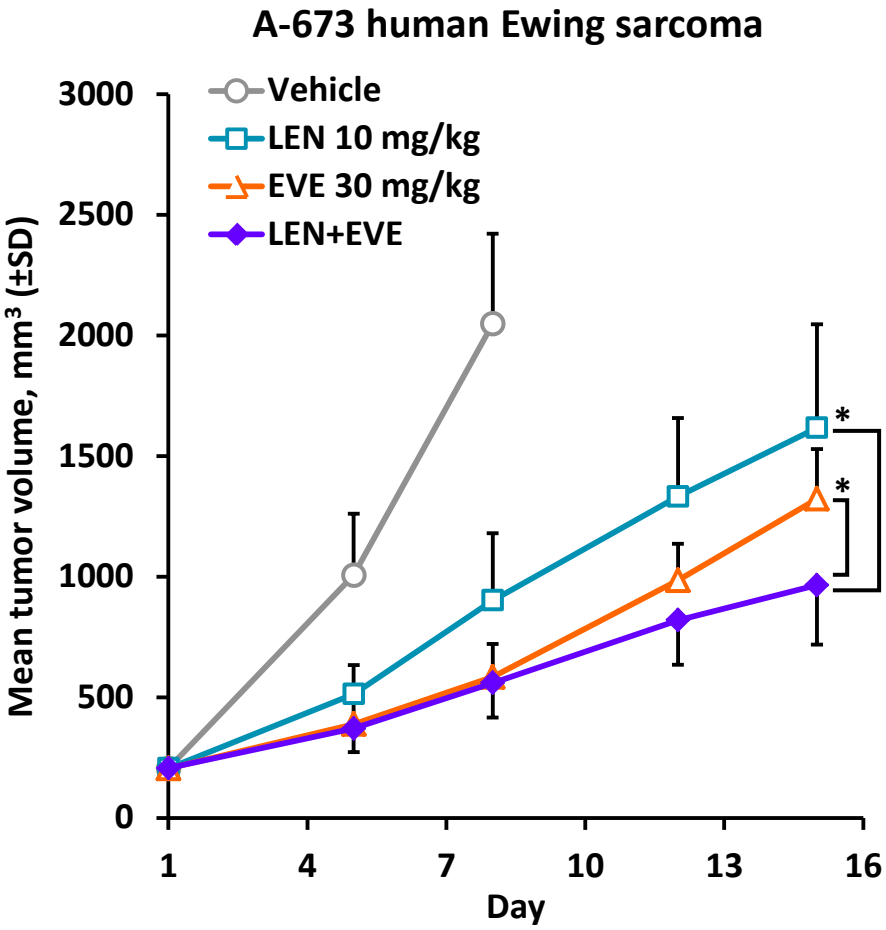
Antitumor Activity Observed in Human Pediatric Osteosarcoma Xenograft Models

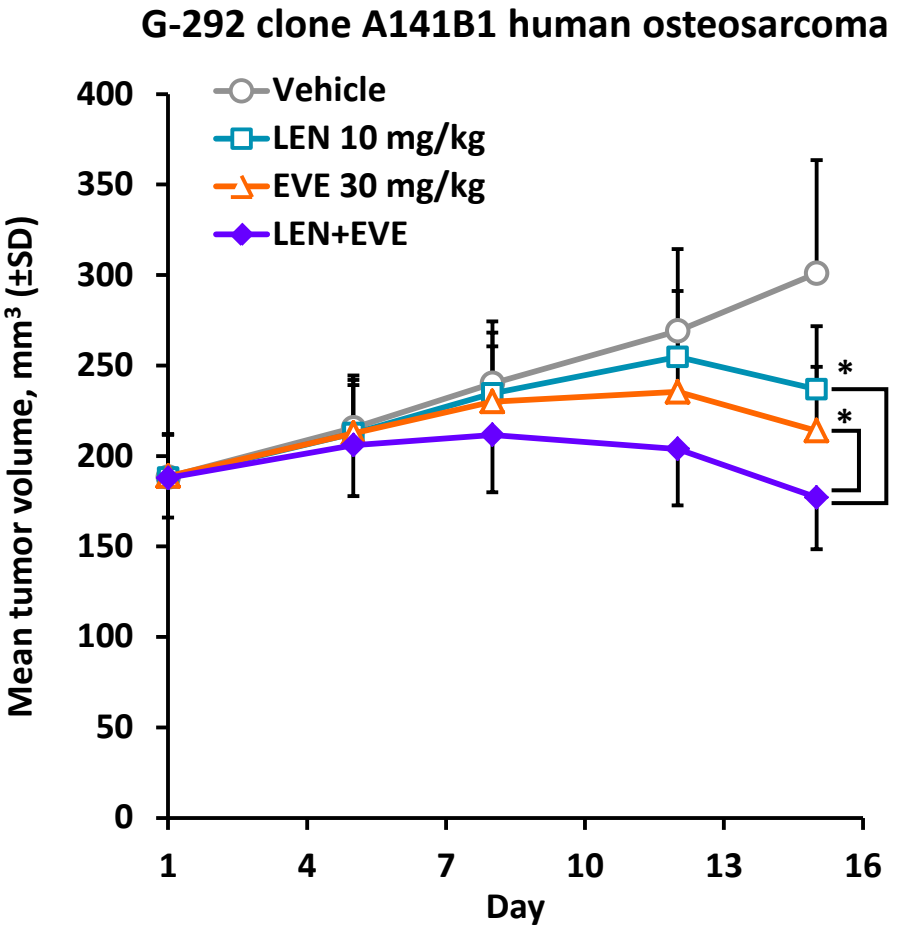
Lenvatinib enhanced antitumor activity of IFM+ETP in 3 models



ETP=etoposide; IFM=ifosfamide; LEN=lenvatinib.

Antitumor Activity of Lenvatinib + Everolimus in Human Pediatric Sarcoma Xenograft Models





* P<0.05 Dunnett's test.

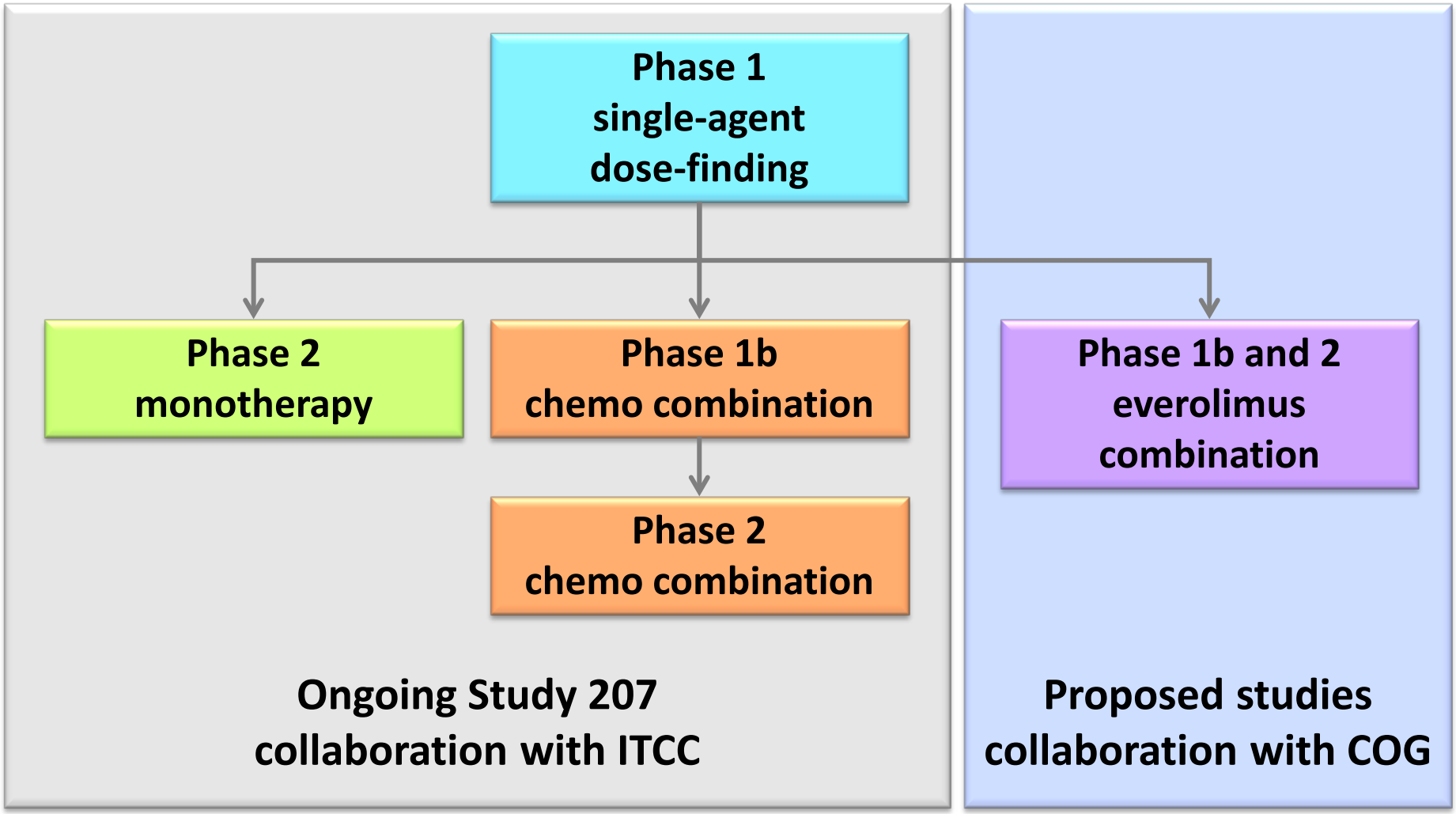
Comprehensive Preclinical Investigation Plan to Support Tumor Types in Proposed COG Studies

Tumor type	Pediatric xenograft models completed	Planned pediatric models
Osteosarcoma	G-292 clone A141B1	**6 PDX xenograft models** In discussion with Dr. Richard Gorlick, Children's Hospital at Montefiore
Ewing sarcoma[a]	A-673	**2 cell lines/xenograft models** In discussion with Dr. Dela Cruz, CPMC
Soft tissue sarcoma Rhabdomyosarcoma Synovial sarcoma	None	**2 - 3 PDX xenograft models** In discussion with Dr. Dela Cruz, CPMC
High-grade glioma[a]	None	**2 cell lines/xenograft models** In discussion with Dr. Dela Cruz, CPMC

PDX=patient-derived xenograft.

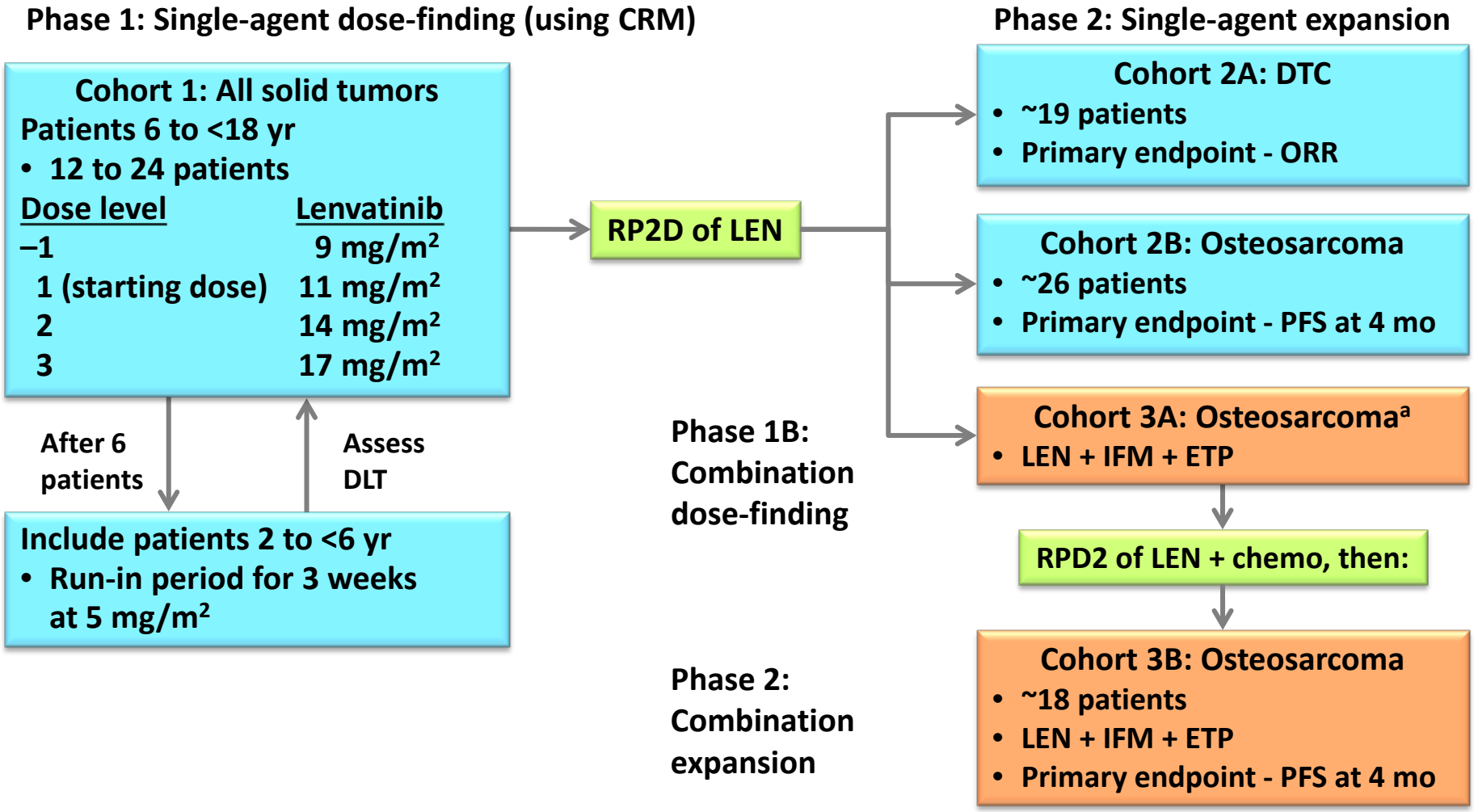
[a] In parallel, efforts will be made to identify patient-derived models for Ewing sarcoma and high-grade glioma.

Lenvatinib Pediatric Development Program



Ongoing Pediatric Study

Study 207 (Collaboration With ITCC)



CRM=continuous reassessment method; ETP=etoposide; IFM=ifosfamide, LEN=lenvatinib.

[a] Lower levels of LEN will be explored.

Safety Monitoring in Pediatric Program

Safety parameter	Monitoring plan
Bone growth	X-rays: BL and EOT Height: BL, D1 each cycle, EOT, post-treatment
Cardiovascular events	ECG: BL, D1 each cycle, EOT ECHO: run-in, every 16 weeks, EOT
Diarrhea	Symptomatic management
Hypertension	ITCC or COG protocol
Proteinuria	Urine dipstick: BL, weekly cycle 1-3, then biweekly, EOT
Renal function	Creatinine: BL, run-in, D1 & D15 cycle 1-3, D1 thereafter, EOT

Current Status on November 9, 2015

Study 207 Cohort 1 (Dose-Finding)

Tumor type	Age, yr	Dose level, mg/m^2	Status/reason for discontinuation[a]	Best overall response[b]
Rhabdomyosarcoma	17	11	Radiographic PD (Cycle 6, Day12)	SD
Osteosarcoma	12	11	Radiographic PD (Cycle 4, Day 28)	SD
Epithelioid sarcoma	17	14	Radiographic PD (Cycle 1, Day 17)	PD
Undifferentiated sarcoma	15	14	Ongoing in Cycle 6	SD
Ewing sarcoma	15	14	Clinical PD (Cycle 2, Day 23)	PD
Ewing sarcoma	15	14	Ongoing in Cycle 6	SD
Alveolar rhabdomyosarcoma	12	17	Radiographic PD (Cycle 2, Day 28)	PD
Paraganglioma	17	17	Ongoing in Cycle 5	SD[c]
Alveolar rhabdomyosarcoma	14	17	Radiographic PD (Cycle 2, Day 28)	PD
Rhabdomyosarcoma	11	17	Radiographic PD (Cycle 2, Day 20)	—
Neuroblastoma	10	17	Ongoing in Cycle 2	—
Rhabdomyosarcoma	6	17	Ongoing in Cycle 2	—
Ewing sarcoma	12	17	Ongoing in Cycle 2	—
Medulloblastoma	15	17	Ongoing in Cycle 1	—
Alveolar soft-part sarcoma	16	17	Ongoing in Cycle 1	—

[a] One treatment cycle is defined as a 28-day period.
[b] Radiographic best overall response by MRI as reported by the investigator.
[c] Investigator reported a complete MIBG response after 2 cycles.

Preliminary Safety Data

Study 207 Cohort 1 (Dose-Finding)

- Adverse events mostly grade 1/2
- No treatment-related grade 3/4 AEs[a]

Sarcoma type	Dose level, mg/m^2	SAE[b]
Osteo	11	Metastases to pleura, respiratory distress[c]
Epithelioid	14	Worsening of cancer pain[c] Grade 4 lipase increased[c] Grade 4 serum amylase increased[c]
Undifferentiated	14	Pneumonia
Ewing	14	Colitis, cardiac arrest[c]
Rhabdomyo	17	Disseminated intravascular coagulation, pleural effusion[c]

[a] Data Cut-off: October 19, 2015.
[b] Data Cut-off: November 9, 2015.
[c] Events were due to disease progression.

Proposed Pediatric Studies

Collaboration With Children's Oncology Group

Phase 1b
Recurrent/refractory solid tumors, including CNS tumors

Lenvatinib + everolimus
(dose-escalation)
~36 pts
(rolling 6 design)

Phase 2
Simon's optimal 2-stage design

- Osteosarcoma (19-32 pts)
- Ewing sarcoma/peripheral pNET (10-22 pts)
- Rhabdomyosarcoma (10-22 pts)
- High-grade glioma (10-22 pts)

Descriptive (up to 15 pts)

- RAI non-avid/RAI-refractory DTC

Clinical Data Generated by Pediatric Program

	Treated patients
Total	**134 - 277**
By treatment regimen	
Lenvatinib monotherapy	12 - 69
Lenvatinib + chemotherapy	6 - 30
Lenvatinib + everolimus	53 - 178
By tumor type	
Sarcoma	89 - 132
Other solid tumors	45 - 145

Basis for a Written Request

- Data from Study 207 and proposed COG studies should be sufficient for a written request
  - Data provide an adequate pediatric safety database
  - Sufficient data to be included in the label
  - Efficacy data sufficient to allow COG to decide whether a phase 3 survival study is warranted

Summary and Conclusions

- Lenvatinib is a novel RTK inhibitor
- Impressive efficacy with manageable safety profile in adult solid tumors
- Can be safely combined with everolimus
- Promising phase 2 combination data in RCC
- Preclinical activity in sarcoma models
- Pediatric study ongoing
- Proposed collaboration with COG
- Data sufficient to support a written request

Fatal Adverse Events (On Study)

Study 303

Preferred term	Study day of adverse event onset	Treatment duration, days	Day of death in relation to last dose[a]
Lenvatinib			
Acute respiratory failure	83	81	2
Myocardial infarction	51	41	10
Death[b]	459	441	18
Pulmonary embolism	140	139	1
Death[b]	102	94	8
General physical health deterioration	32	24	8
Pneumonia/sepsis	14	9	5
Pulmonary embolism	171	159	12
Sudden death	15	15	0
Lung infection	101	89	12
Hemorrhagic stroke	76	76	1
Placebo			
Myocardial infarction	52	52	0
Sudden death	194	194	0
Sepsis	149	145	4

Patients who died due to PD or had an ongoing fatal AE at the time of death due to PD are not included.
3 patients with death due to PD unknown are also included.
[a] Number of days between end of treatment with study drug and death.
[b] Death occurred within 30 days of the last dose of study drug.

Study 303 CSR (15 Nov2013) Table 37.

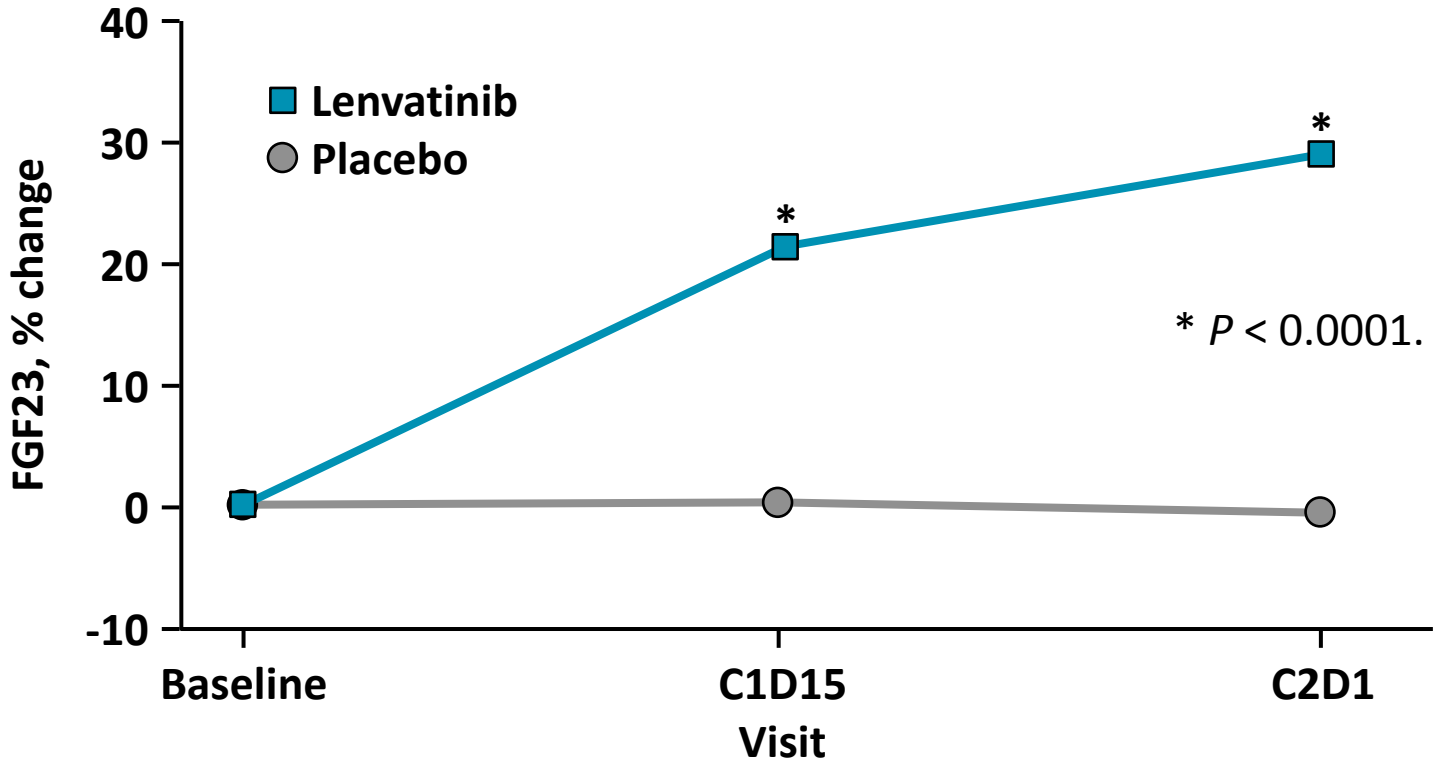
Impaired Wound Healing

	Patients, n (%)	
	All DTC pts treated with lenvatinib N=458	RCC pts treated with LEN + EVE N=62
Patients with ≥1 TEAE	6 (1.3)	0
Adjusted by treatment duration (AE rate)[a]	6 (<0.01)	0
Maximum CTCAE Grade		
1	4 (0.9)	0
2	1 (0.2)	0
3	1 (0.2)	0
4	0	0
SAEs[b]	1 (0.2)	0
TEAEs leading to treatment discontinuation	1 (0.2)	0
TEAEs leading to study drug modification	1 (0.2)	0
Reduction	0	0
Interruption	1 (0.2)	0

[a] Total treatment duration, 608.1 years.
[b] Grade 3 SAE ongoing.

Post-treatment Increase in FGF23 Levels with Lenvatinib Compared with Placebo

Study 303



- FGF23 levels were increased by 20.8% and 28.6% at C1D15 and C2D1 with lenvatinib, respectively
- FGF23 levels did not change with placebo treatment (0.1% and -0.7% at C1D15 and C2D1 compared to baseline, respectively)

Key Findings in Pivotal Juvenile Rat Toxicology Study – Dosing Initiated on PND21

- Effected target organs similar to adult rats and include:
  - **Kidney** – glomerulopathy, proteinuria, increased BUN
  - **Vascular system** – arterial fibrinoid necrosis, medial degeneration, or hemorrhage
  - **GI tract** – soft/watery stool, inflammation, mucosal atrophy
  - **Bone** – widening of the epiphyseal growth plate, incisor changes (rat only)
  - **Reproductive organs** – ovarian follicular atresia, testicular hypocellularity
- Mortality at 10 mg/kg observed earlier than in adult rats
- Growth retardation and secondary delay of physical development
- Most findings reversible at the end of the 4-week recovery period

Efficacy in Recurrent Brain Tumors

Study 203

	Cohort 1 Bev-naive GBM		Cohort 2 Bev-naive Grade 3 MG	Cohort 3 GBM failed prior bevacizumab
	Lenvatinib N=42	Bevacizumab N=38	Lenvatinib N=39	Lenvatinib N=32
6-month PFS rate, %	21.2	11.0	8.0	7.6
Objective response rate, %	21.4	15.8	7.7	0

GBM=glioblastoma; MG=malignant glioma; PFS=progression-free survival.

Reardon et al ESMO , 2012, Vienna.

Antiproliferation and Anchorage-Independent Growth of G-292 Clone A141B1 Osteosarcoma Cell Line

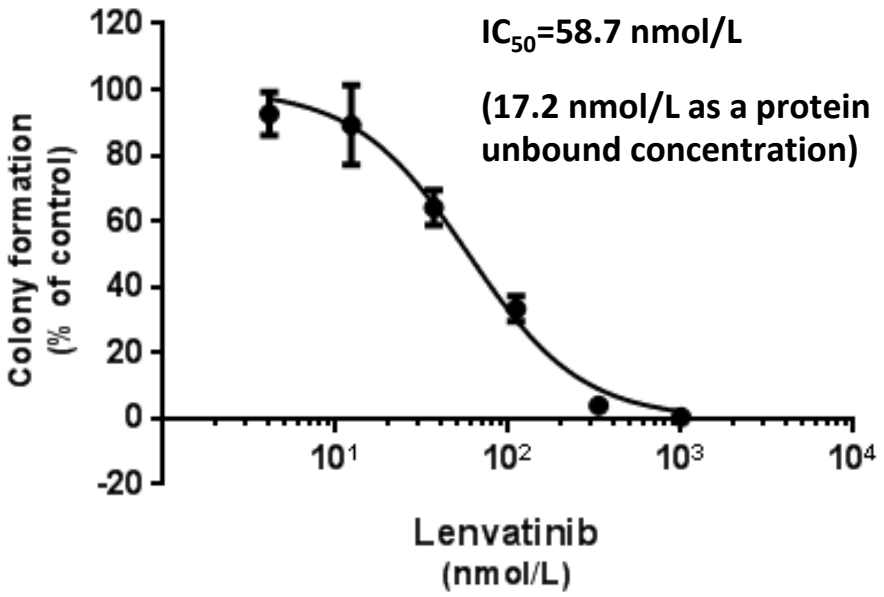
G-292 clone A141B1 harbors FGFR1 amplification

Anti-proliferative activity

Cell name	IC_{50}, µM	
	Lenvatinib	Etoposide
143B	>10	0.74
G-292 clone A141B1	1.3	4.10
HOS	>10	0.47
Saos-2	>10	1.80
Hu09	>10	0.31

Anchorage-independent growth of G-292 clone A141B1

Data expressed as mean of 6 wells ± SEM



Incidence and Severity of Diarrhea

Study 303: DTC

	Patients, n (%)	
	Lenvatinib 24 mg N=261	Placebo N=131
Overall incidence, all grades	176 (67.4)	22 (16.8)
Adjusted by treatment duration, episodes per pt-yr	1.51	0.39
Grade 3 diarrhea[a]	24 (9.2)	0
Leading to dose interruption/ reduction, all grades	59 (22.6)	0
Leading to treatment discontinuation (all grades)	0	0
SAE of diarrhea	2 (0.8)[b]	0
Median time to first onset, weeks	13.1	3.7
Median duration, days	11	8

[a] No Grade 4 or Grade 5 events of diarrhea were reported,
[b] 1 patient hospitalized.

DTC ISS, Table 5.3.0, Table 5.3.0.1, Table 5.4.0, Table 6.4.0, Table 6.1.0, Table 8.1.

Incidence of Diarrhea

Study 205: RCC

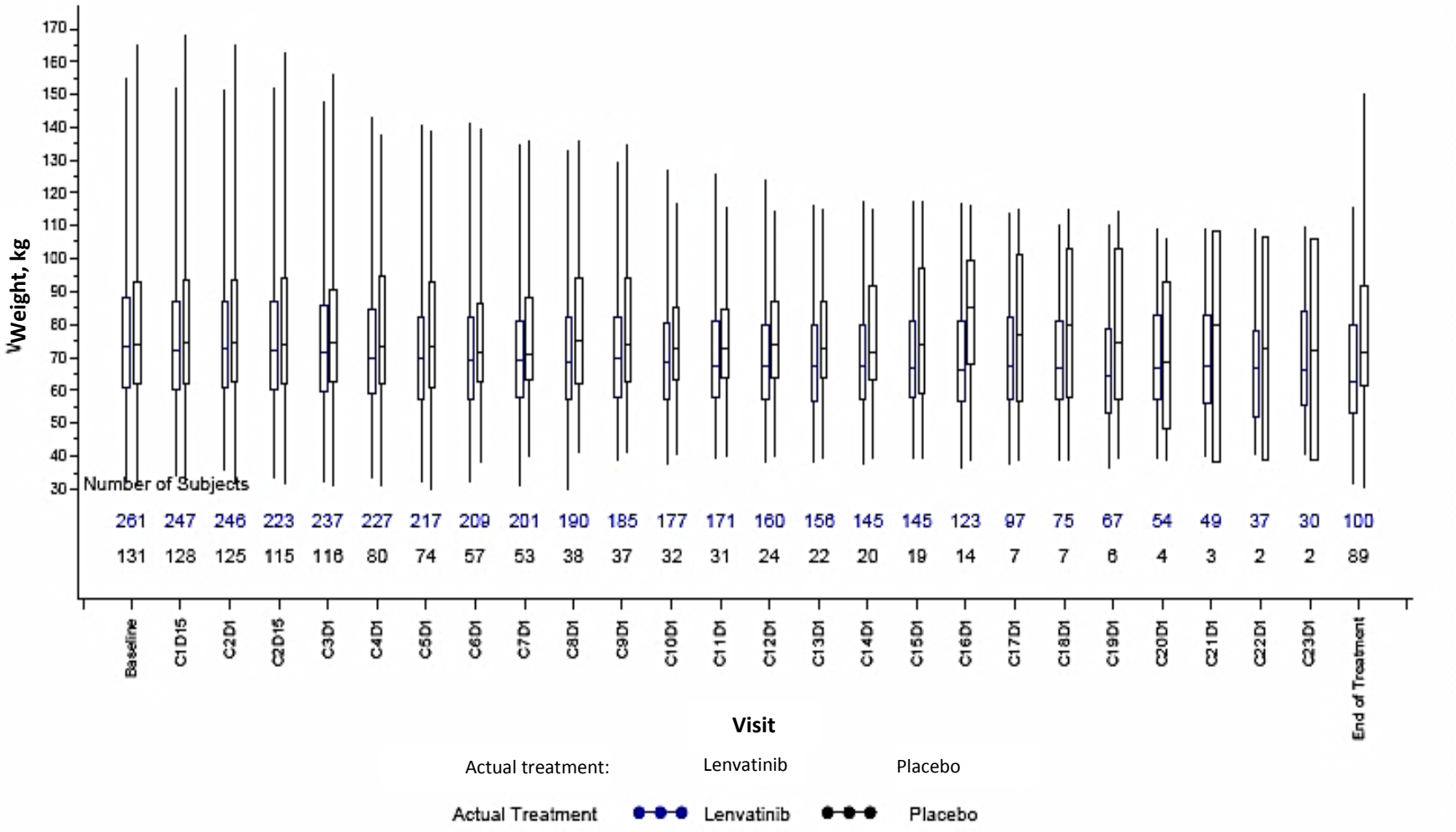
	Patients, n (%)		
	Lenvatinib 18 mg + Everolimus 5 mg N=51	Lenvatinib 24 mg N=52	Everolimus 10 mg N=50
Overall incidence, all grades	43 (84.3)	37 (71.2)	17 (34.0)
Adjusted by treatment duration, episodes per pt-yr	3.6	2.4	0.8
Grade 3 diarrhea[a]	10 (19.6)	6 (11.5)	1 (2.0)
Any grade diarrhea, dose interruption/reduction	23 (45.1)	15 (28.8)	1 (2.0)
Grade 3 diarrhea, dose interruption/reduction	6 (11.8)	5 (9.6)	1 (2.0)
Leading to treatment discontinuation, all grades	1 (2.0)	0	0
SAE of diarrhea	3 (5.9)[b]	0	0
Median time to first onset, weeks	4.1	6.1	4.1
Median duration, days	6	21	3

[a] No Grade 4 or Grade 5 events were reported.

[b] Two Grade 3, one Grade 2; all 3 patients hospitalized and recovered.

Body Weight by Visit

Study 303: DTC



Reported Frequency of Hypothyroidism Associated With Other VEGFR TKIs

	Reported frequency of hypothyroidism, %
Axitinib	83-92
Sunitinib	53-85
Vandetanib	89
Sorafenib	20-36
Motesanib	22
Pazopanib	10-29
Tivozanib	5
Lenvatinib	**5-37**

Ahmadieh H and Salti I. *BioMed Res Int*. 2013;2013:E-pub.

Measures of Efficacy – Simon Stage 2 Design

Proposed COG Studies

- **Osteosarcoma**
  - **Stage 1**: 19 evaluable pts
    - Outcome measures: ORR (RECIST 1.1) and 4-month PFS rate
    - If ≤1 response AND ≤4 pts progression free at 4 months, the cohort will be terminated; otherwise proceed to stage 2
  - **Stage 2**: 10 additional evaluable pts will be enrolled (to total of 29 patients)
    - If ≤4 responses AND ≤8 pts progression free at 4 months among 29 evaluable pts, the lenvatinib/everolimus combination will be declared a failure
- **Ewing Sarcoma/Peripheral PNET, Rhabdomyosarcoma, and High-Grade Glioma**
  - **Stage 1**: 10 evaluable pts
    - Outcome measure: ORR (RECIST 1.1)
    - If no responses among first 10 pts, the cohort will be terminated, otherwise proceed to Stage 2
  - **Stage 2**: 10 additional evaluable pts will be enrolled (to total of 20)
    - If ≤2 responses among 20 evaluable pts, the lenvatinib/everolimus combination will be declared a failure for that disease cohort

Statistical Assumptions

Study 207

Cohort 1 (single-agent dose-finding)

- Recommended dose defined as the dose that has a DLT rate closest to the targeted 20% rate

Cohort 2 (single-agent expansion)

- Cohort 2A: DTC (N=19; 80% power)
  - Null hypothesis that ORR is ≤5% will be tested against the alternative hypothesis of an ORR ≥20%
- Cohort 2B: Osteosarcoma (N=26; 80% power)
  - Null hypothesis that 4-month PFS rate is ≤25% will be tested against the alternative hypothesis of a 4-month PFS rate ≥45%

Cohort 3 (chemotherapy combination expansion)[a]

- Cohort 3B (osteosarcoma) (N=18; 80% power)
  - Null hypothesis that 4-month PFS rate is ≤25% will be tested against the alternative hypothesis of a 4-month PFS rate ≥50%

[a] Osteosarcoma patients who progress in Cohorts 1 or 2B can opt to receive combination therapy; however, statistical assumptions are only based on lenvatinib-naive patients.

Efficacy Results
Study 208

Summary of Efficacy: Progression-Free Survival, Overall Survival, and Objective Response Rate by Histology and Total

	Patients with events, n (%)			
	RR-DTC (N=23)	MTC (N=9)	ATC (N=11)	Total (N=43)
Median progression-free survival, months (95% CI)	NE	7.3 (1.8, NE)	7.4 (1.9, NE)	NE (7.4, NE)
Median overall survival, months (95% CI)	NE	12.1 (3.8, NE)	10.6 (3.9, NE)	NE
Objective response rate, n (%) (95% CI)	16 (69.6) (47.1, 86.8)	1 (12.5) (0.3, 52.7)	3 (27.3) (6.0, 61.0)	20 (47.6) (32.0, 63.6)
Stable disease, n (%)	7 (30.4)	7 (87.5)	7 (63.6)	21 (50.0)
Progressive disease, n (%)	0	0	1 (9.1)	1 (2.4)

	mPFS	mOS	ORR	Reference
Carboplatin + Paclitaxel (N=25)	3.1 Months	4.0 Months	16%	Sosa et al. *Thyroid*. 2014;24:232.
Sorafenib (N=20)	1.9 Months	3.9 Months	10%	Savvides et al. *Thyroid*. 2013;23: 600.

Source: